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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NR 00003-01 HRHI

PERIOD COVERED

October 1, 1991 to September 30, 1992

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Burden, Quality of Life of Elderly Caregivers in Alzheimer's Disease (N01-HC-05102)

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Carolyn L. Murdaugh Contract Federal Advisor
Chief, Laboratory for the Study of Human Response to Health and Illness (HRHI)

COOPERATING UNITS *(if any)*

NCNR; NHLBI (Honolulu Heart Program) with Kuakini Medical Center, Honolulu, HI; NIA

LAB/BRANCH

Laboratory for the Study of Human Response to Health and Illness (HRHI)

SECTION

INSTITUTE AND LOCATION

NCNR, NIH; Building 31, Room 5B10; 9000 Rockville Pike; Bethesda, MD 20892

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
1.0	1.0	Contract

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Predictors of caregiver burden and quality of life in elderly caregivers of persons with Alzheimer's Disease (AD) are being studied in the Honolulu Asian Aging Study of the Honolulu Heart Program. The caregivers are elderly spouses or siblings of elderly Japanese American men who reside in Hawaii.

In a longitudinal study, 200 caregivers of persons with AD and 200 spouses of a control group are participating in both face to face and telephone interviews every three months for two years. Information collected about the caregiver includes demographic information, acculturation, perceived control, social networks, social support, health status, health service use, burden, coping strategies, depression, functional status, life satisfaction, and social well-being. Information collected about the demented person includes driving behaviors, self-care behaviors, health status, health service use, and progression of dementia behaviors. Data collection has been underway since March 31, 1992 and will continue until December 1994.

The significance of this study lies in the identification of variables that are predictive of caregiver burden and quality of life for elderly women. Interventions can then be developed to decrease burden and enhance the quality of life of elderly women who care for a demented spouse.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NR00002-01 CTL

PERIOD COVERED

October 1, 1991 to September 30, 1992

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Myopathy During Prolonged Antiretroviral Therapy for HIV Infection (91-I-142)

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: Mary E. Ropka, Associate Director for Intramural Research, NCNR
Others: Christine Grady, Research Associate, CTL/NCNR
Karen Hench, Senior Research Nurse, CTL/NCNR

COOPERATING UNITS *(if any)*

1. LIR/NIAID
2. MN/NINDS
3. Clinical Center Department of Nursing

LAB/BRANCH

Clinical Therapeutics Laboratory (CTL)

SECTION

INSTITUTE AND LOCATION

NCNR, NIH, Bethesda, MD 20892

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
1.0	1.0	

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The two major **aims** of this study are to: (1) Describe and compare the histopathologic characteristics; serum biochemical features; and condition-specific clinical performance, functional status, and health perceptions of patients who have developed myopathy during antiretroviral therapy for HIV infection; and (2) Contrast the changes in histopathologic characteristics; serum biochemical features; and myopathy-related clinical performance, functional status, and health perceptions that occur over time, and following clinically-determined interventions such as altered antiretroviral doses, steroid administration, or nonsteroidal anti-inflammatory medications. In addition, it explores differences in responses to general and newly developed condition-specific items of an adapted version of the Short Form of the Medical Outcomes Study questionnaire (SF-36 MOS) in order to determine health perceptions and health status as judged by the patient.

A concurrent, prospective case series **design** is used which involves longitudinal measurement of most study variables at monthly intervals for the original six month duration of the study, with the exception of muscle biopsy which is performed at the beginning and then repeated once. One additional evaluation at around 12 months has been added. 25 evaluable subjects have been recruited, involving consecutive patients participating in NIAID HIV treatment trials who meet the study criteria.

Laboratory studies performed at baseline and monthly for six months include: CBC with differential; Acute Care, Hepatic, and Mineral Panels; CK; LDH; Aldolase; Lactate; and Urinalysis. Clinical performance is evaluated at baseline and monthly for six months by manual muscle strength testing, while functional status is assessed by timed muscle activities and functional grade. Health perceptions and health status are measured by the MOS questionnaire.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NR00001-02 CTL

PERIOD COVERED

October 1, 1991 to September 30, 1992

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Nutritional Changes During HIV Treatment, Relation to Immune Function (90-I-156)

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: Mary E. Ropka, Associate Director for Intramural Research, NCNR
Others: Robin Anderson, Senior Research Nurse, CTL/NCNR
Christine Grady, Research Associate, CTL/NCNR

COOPERATING UNITS *(if any)*

1. LIR/NIAID
2. Clinical Center Department of Nursing
3. Clinical Center Nutrition Department

LAB/BRANCH

Clinical Therapeutics Laboratory (CTL)

SECTION

INSTITUTE AND LOCATION

NCNR, NIH, Bethesda, MD 20892

TOTAL STAFF YEARS:	PROFESSIONAL:	OTHER:
1.1	1.1	

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This study **aims** to: (1) Describe the type and extent of changes in nutritional status that develop across the spectrum of HIV infection during its treatment, including etiology of nutritional changes and adequacy of nutritional intake; changes in body composition by weight and other anthropometric measures and bioelectrical impedance analysis (BIA); biochemical parameters associated with nutritional status or suggested to be associated with HIV infection (cholesterol, triglycerides, vitamin B12, and folate); and (2) Explore the extent to which nutritional status serves as a cofactor to impaired immune function during HIV infection and its treatment. The effect of timing and pattern of collecting dietary intake information on diversity of reported intake and dependability of reporting will also be determined.

Initiated in July 1990, the study employs an initial cross-sectional **design**, comparing different HIV disease severity groups determined by CD4 count and HIV treatment protocols, combined with a longitudinal **design**, involving follow-up of subjects at monthly intervals for the first eight months and then at decreasing intervals. Recruitment was completed in May 1992, including 120 subjects of whom 13 were females.

In response to early observations regarding the absence of anticipated measurable levels of Tumor Necrosis Factor (TNF), two substudies were conducted in collaboration with LIR/NIAID. In addition, two other substudies were conducted. The first evaluated the consequences of the observed inability of subjects to not eat or drink prior to BIA on the accuracy of body composition estimates by BIA. The second measures energy consumption by indirect calorimetry in order to validate estimates of energy requirements with these more precise indirect calorimetry measures.

NATIONAL CENTER FOR NURSING RESEARCH
DIVISION OF INTRAMURAL RESEARCH PROGRAMS
STUDY UPDATE: OCTOBER 1, 1992

TITLE: "A Study of Caregiving and Quality of Life in Aging and Dementia"

NCNR INTRAMURAL PROJECT NUMBER: Z01 NR 00003-01 HRHI

MAJOR AIMS:

1.0 Describe the major predictors and consequences of caregiver burden and quality of life in female caregivers of elderly men with dementia and significant others of elderly men with normal cognitive function.
   1.1 Predictors include:
   Demographic factors, cognitive status, acculturation, perceived control, coping strategies, family network, social network, social support.
   1.2 Consequences include:
   Caregiver burden, global health status, functional status, sleep, health service use, depression, social well-being, leisure activities, life satisfaction.
2.0 Describe changes in predictors and consequences of caregiver burden and quality of life over the course of the illness (progression of dementia).
3.0 Describe the relationship between dementia behaviors of the elder and caregiver consequences over the course of the illness.
   3.1 Describe the relationship between the progression of dementia behaviors and caregiver consequences over the course of the illness.
4.0 Describe the caregiver and elder predictors of institutionalization of the demented elder.
   4.1 Caregiver predictors include:
   Demographic factors, cognitive status, family network, social support, coping strategies, perceived control, objective and subjective burden, health status, functional status, depression, life satisfaction, social well-being, and global health status.
   4.2 Elder predictors include:
   health status, health services use, progression of dementia behaviors.
5.0 Describe the caregiver consequences of institutionalization of the demented elder.

INVESTIGATORS:

Carolyn Murdaugh, RN, PhD/NCNR; Lon White, MD/NIA; Webb Ross, MD/Veterans Administration; Jane Kadehiro, RN, MA, Carol Trockman, RN, BS/Nurse Investigators; Helen Petrovich, MD/Co-Principal Investigator, Honolulu Aging and Dementia Study; David Curb, MD/Principal Investigator, Honolulu Heart Program

METHODS:

Design:

- Descriptive, longitudinal design comparing caregivers of a demented group and significant others of a non-demented comparison group at baseline and every three months for two years.

Estimated Sample Size:

- Demented Group: N = 200
  Comparison Group: N = 200

Sampling:

- All Caregivers and Significant Others of elders who have been randomly selected from a sample of Honolulu Heart Study participants which has been stratified on cognitive assessment score, age and education.

Measurement:

- Predictors:
  Blessed Dementia Scale (Blessed 1968)
  IQCODE (Jorm 1988)
  Social Network Scale (Cornoni-Huntley et al 1986)
  Social Support Scale (Woods & Parham 1990)
  Family Network Scale (Cornoni-Huntley 1986)
  Perceived Control Index (Pagel, Becker & Coppel 1985 modified)
  Revised Ways of Coping Scale (Felton et al 1984)

- Consequences:
  Caregiver Burden Index (Novak & Guest 1989)
  Depression CES-D (Radloff 1977)
  Social Participation Scale (George & Gwyther 1986)
  Life Satisfaction Ladder (Cantril 1972)
  Functional Status Questionnaire (Lawton 1982 modified)
  Global Health Status (Idler & Kasl 1991)
  Health Services Use Questionnaire (Cornoni-Huntley et al 1986)
  Sleep

- Dementia Behaviors:
  Behavioral Problem Checklist (BPC) (Niederehe 1988)
  Driving Behaviors Questionnaire (modified)

  In addition, information collected in both the HHP Examination 4 and the Aging and Dementia Module II Level I and Level II examinations are accessible.

PROGRESS TO DATE:

Accrual:

- Data Collection initiated May 1, 1991.
- Data Collection interviews as follows:
  Module II Level I Baseline visits: (Potential Caregivers) N = 512
  The following information has been collected on potential CG/SO.
  - Demographic Data
  - Acculturation
  - Cognitive Assessment
  - Social Networks
  - Social Support
  - Health Status
  - Health Service Use
  - Depression
  - Social Well-Being
  - Life Satisfaction

- Subjects entered into study as of September 18, 1992.

Referrals to Demented Group:		N = 173
Demented Group (Dx of Dementia) by Consensus Conference		N = 49
Control Group:		N = 98
Demented Group:	Home Visits	N = 49
	Follow-Up Contact	N = 35
Control Group:	Initial Contact	N = 81
	Follow-Up Contact	N = 124

Autopsy Follow Up:

- A protocol has been developed in collaboration with the Surveillance Nurse to facilitate obtaining permission for autopsy of the participant death. The nurse investigators will communicate with the surveillance nurse on a regular basis to prevent loss of patient follow up for autopsy.

Analysis:

- Currently all of the data collected are entered into the computer data bank on an ongoing basis from Form 1 (Clinic visit), Form 2, and Form 3 charts.

Early Findings:

- None.

Personnel & Organizational:

- Currently Jane Kadehiro, Nurse Investigator is 50% time. A second nurse investigator, is 100% time. The two nurse investigators are responsible for project operations, including data collection.

SIGNIFICANCE TO BIOMEDICAL RESEARCH AND NCNR:
The charge of the intramural research laboratory for the Study of Human Responses to Health and Illness is to conduct investigations which focus on the biophysiologic and behavioral aspects of human responses that occur in health and illness, including (a) processes, mechanisms and environments that influence health, health-promoting and health-maintaining behaviors; (b) interventions that reduce the risk of illness as well as minimize impairments or complications that result from disease, health conditions or injuries; and (c) interventions that facilitate adjustment to illness or disability. The Honolulu Heart and Aging Research on Caregiving and Quality of Life in Dementia addresses critical questions related to caregiving and quality of adults caring for a person with a chronic illness. The information gained will enable the investigators to develop and test interventions to decrease burden and improve the health and quality of life for elderly female caregivers.

PROPOSED COURSE:
Data collection will terminate September 30, 1993. The current contract expires 12/31/93.

PUBLICATIONS:
None.

COLLABORATION:

- The study is a component of the Honolulu Heart Program Study on Aging and Dementia in Honolulu, Hawaii. The Principal Investigator for the HHP is David Curb, MD.

FUTURE PLANS:

- Data collection will be continued into 1995 to complete the follow up on all of the CG/SO in the study. The remainder of 1995 will focus on data analysis and write up. In addition, plans are underway to continue the nursing research component during Module 3, with NIA. An outline of the proposed continuation study is currently under review.

November 5, 1992 rs
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NATIONAL CENTER FOR NURSING RESEARCH
DIVISION OF INTRAMURAL RESEARCH PROGRAMS
STUDY UPDATE

TITLE: "A Combined Cross-sectional and Longitudinal Study to Evaluate Nutritional Changes Occurring During Treatment for HIV Infection, and Their Relationship to Immune Function" (#90-I-156)

NCNR INTRAMURAL PROJECT NUMBER: Z01 NR 00001-02 CTL

MAJOR AIMS:

1.0 Describe the type and extent of changes in nutritional status, both nutritional excesses and deficits, that develop across the spectrum of HIV infection during its treatment.
   - 1.1 Determine the etiology of nutritional changes by assessing the adequacy of nutritional intake in terms of calories and protein, altered digestion and absorption, metabolic changes, and extent of excessive nutrient loss.
   - 1.2 Evaluate body composition, including the composite measure of weight (WT); body fat by skinfold measures (SF) and bioelectrical impedance analysis (BIA); and lean body mass by midarm circumference (MAC) and bioelectrical impedance analysis (BIA).
   - 1.3 Examine biochemical parameters associated with nutritional status, including serum albumin, transferrin, and prealbumin.
   - 1.4 Examine biochemical parameters suggested to be associated with HIV infection, including cholesterol, triglycerides, vitamin B12, and folate.

2.0 Explore the extent to which nutritional status serves as a cofactor to impaired immune function during HIV infection and its treatment by determining the relationship of changes in nutritional status to changes in immune function. Measures reflecting immune function include T-cell subsets, immunoglobulins, and cachectin (TNF).

3.0 SUBSTUDY #1 (planned at the time of the original NCNR study): Evaluate the effect of collecting food record information on three consecutive days including one weekend day as compared to three non-consecutive days including one weekend day on variability of reported food intake and compliance with data collection.

INVESTIGATORS:

Mary E. Ropka, Ph.D., RN; Robin Anderson, M.B.A., RN; Bill Barrick, M.S., RN; Judith Falloon, M.D.; Christine Grady, M.S., RN; Karen Hench, M.S., RN; H. Clifford Lane, M.D.; Joseph A Kovacs, M.D.; Julie Metcalfe; Michael A. Polis, M.D.

METHODS:

Design:

- Cross-sectional, comparing different HIV disease severity groups (identified by onstudy CD4 count) and HIV treatments nested within disease severity protocols.
- Longitudinal, with follow-up of subjects at monthly intervals for the first eight months, then decreasing to three-, four-, or six-month intervals depending on parent study measures.

Estimated Sample Size:

90 evaluable subjects total

Sampling:

- Systematic sampling of 30 eligible subjects from each of 3 HIV disease severity groups (initially represented by NIAID primary studies) as determined by onstudy CD4 counts
- Systematic sampling within the NIAID 3-Arm of 10 subjects from each of 3 treatment groups

Measurement:

- Anthropometric measures: body build, height, weight, skinfold measures, mid-arm circumference, bioelectrical impedance analysis
- Laboratory biochemical studies: serum albumin, serum transferrin, serum prealbumin, cholesterol, triglycerides, vitamin B12, folate
- Dietary intake: 24-hour record of dietary intake for 3 days in a week
- Immune function: T-cell subsets, blastogenesis, NK cell activity, immunoglobulins, TNF
- HIV viral activity: p24 antigen, HIV culture, PCR
- Nutrition-related symptoms: anorexia, nausea/vomiting, oral lesions (stomatitis), dysphagia/odynophagia, diarrhea, fatigue, dyspnea, fever

PROGRESS TO DATE:

Accrual:

- Initiated in July 1990.
- Recruitment completed in May 1992, with 120 patients recruited, 13 of whom are women. Recruitment by CD4 disease severity groups in as follows: 31 from CD4 $<$ 200 (0 females); 32 from CD4 200-500 (5 females); 57 from CD4 $>$ 500 (8 females).
- As of September 1992, 55 people remain on-study, with 65 completed (25 from CD4 $<$ 200; 40 from CD4 $\geq$ 200).

Early findings/observations:

- SUBSTUDY # 2 AND SUBSTUDY #3 (initiated in response to ongoing study findings or observations): To evaluate the absence of anticipated measurable levels of TNF, two substudies were conducted: (1) 16 plasma samples from normal controls were spiked with varying concentrations of recombinant TNF-a and sent to our

contract laboratory (SKB) for standard bioassay. TNF was measurable in the spiked samples; (2) 10 plasma samples, sent to Dr. Guido Poli (LIR/NIAID), were examined for TNF levels by conventional bioassay as well as by incubation with chronically infected cell lines sensitive to TNF induction. No detectable levels of TNF were seen by either of the two methods.

ADDENDUM:
#1: (12/91) To further explore and validate absence of measurable levels of TNF to date, blood obtained from 10 subjects who represent the range of CD4 counts, clinical manifestations, and primary treatment were evaluated in collaboration with Dr. Guido Poli (LIR/NIAID) for: (1) plasma levels of TNF-alpha and TNF-beta; (2) de novo production of TNF-alpha from cells obtained from infected and uninfected (control) individuals; (3) comparison of TNF-alpha plasma levels with de novo production; (4) soluble TNF receptors that might block detection of TNF; and (5) plasma substances with HIV suppressor activity. There were no plasma levels of either TNF-alpha of TNF-beta, but infected cells stimulated with various mitogens produced variable levels of TNF-alpha de novo.

#2: (6/92 - 9/92) SUBSTUDY #4 To evaluate the consequences of the observed inability of subjects to remain NPO prior to BIA, the effect of recent food intake on Bioelectrical Impedance Analysis (BIA) estimates of body composition, specifically related to fluid and/or electrolyte balance, were investigated. BIA was obtained in 20 subjects participating in the Nutrition Study with diverse body builds (1) upon arriving to clinic, in a fasting state; (2) one hour following completion of a standardized breakfast; (3) three hours following completion of the standardized breakfast. This substudy was carried out in the Clinical Center 8th floor AIDS Clinic in collaboration with Celia Hayes and Nancy Sebring, Clinical Center Nutrition Research Specialists. Data analysis is now beginning.

#3: (9/92) SUBSTUDY #5 To correlate nutritional needs and expenditure with nutrient consumption through indirect calorimetry. Of the 54 patients remaining in the Nutrition Study, we will study a subset of 30 patients (approximately ten from each of the three CD4 groupings) using the Sensor Medics Delta Trac Metabolic Monitoring System. Following informed consent, the patient will undergo indirect calorimetry. Expired air drawn in through a hood will be sent through the system for analysis of CO_2 production, oxygen and breathing pattern. This substudy will be carried out in the 8th floor AIDS Clinic, utilizing a metabolic cart owned by the Clinical Center's Department of Critical Care Medicine.

SIGNIFICANCE TO BIOMEDICAL RESEARCH AND THE NCNR:
Increased understanding of the nature, extent, and timing of nutritional problems occurring in individuals during treatment for HIV infection provides a foundation for improved ability to target intensive nutritional assessment and treatment to those at greatest risk in order to ultimately improve duration and quality of survival.

PROPOSED COURSE:
Data collection for the cross-sectional phase is completed with analysis underway. The longitudinal phase involves continued follow-up of all subjects remaining on-study, for up to three years.

PUBLICATIONS:
None.

COLLABORATION:
Carried out in the Clinical Center 8th floor AIDS Clinic through collaboration with NIAID scientists and Study Coordinators, and Clinical Center Nursing AIDS Clinic Case Managers and Nutrition Department.

COMMENTS:
Study developed by NCNR based on identification of major scientific opportunities and systematic review of the state-of-the-science.
In order to answer new NCNR questions, NCNR primary data are obtained in addition to selected NIAID study data.

November 5, 1992;rs
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NATIONAL CENTER FOR NURSING RESEARCH
DIVISION OF INTRAMURAL RESEARCH PROGRAMS
STUDY UPDATE

TITLE: "Histologic, Serologic, and Clinical Characteristics of Myopathy Occurring During Prolonged Antiretroviral Therapy for HIV Infection" (#91-I-142)

NCNR INTRAMURAL PROJECT NUMBER: Z01 NR 00002-01 CTL

MAJOR AIMS:

1.0 Describe and compare the histopathologic characteristics; serum biochemical features; and condition-specific clinical performance, functional status, and health perceptions of patients who have developed myopathy during antiretroviral therapy for HIV infection.

2.0 Contrast the changes in histopathologic characteristics; serum biochemical features; and myopathy-related clinical performance, functional status, and health perceptions that occur over time, and following clinically-determined interventions such as altered antiretroviral doses, steroid administration, or nonsteroidal anti-inflammatory medications.

3.0 SUBSTUDY #1: Explore differences in responses to general and newly developed condition-specific items of an adapted version of the Short Form Medical Outcomes Study (SF-36 MOS) to determine health perceptions and health status. (Involves collaboration with Dr. John Ware at the New England Medical Center.)

INVESTIGATORS:

Principal Investigator:	Mary E. Ropka, Ph.D., RN	DIR/NCNR
Associate Investigators:	Cheryl Jay, M.D.	MN/NINDS
	Christine Grady, M.S, RN	DIR/NCNR
	Marinos Dalakas, M.D.	MN/NINDS
	Karen Hench, M.S., RN	DIR/NCNR
	Judith Falloon, M.D.	LIR/NIAID
	Ed Cupler, M.D. (as of 7/92)	MN/NINDS

METHODS:

Design:

- Concurrent, prospective case series involving longitudinal measurement of most study variables at monthly intervals for the six-month duration of the study, with the exception of muscle biopsy which will be performed at the beginning and then repeated once.

Estimated Sample Size:

25 (increased from 15 to 25 with ICRS approval 12/91) (increased from 15 to 25 evaluable with ICRS approval 10/92)

Sampling:

- Consecutive NIAID study subjects who meet the eligibility criteria.
- Eligibility criteria: enrolled in an NIAID protocol; recent treatment with zidovudine, ddI, ddC or interferon-alpha for a minimum of four months with the last dose within 7 days prior to enrollment; presence of myopathy established according to selected criteria that involve specific physical examination, history of muscle weakness, or laboratory findings in order to operationally define the expert clinical judgement usually required in diagnosing myopathy. Detailed major and minor criteria are specified.
- Exclusion criteria: illicit drugs, neurologic diseases, or endocrine conditions that would complicate evaluation of the study variables; exposure to known myotoxins; family history of muscle diseases; severe malnutrition; eosinophilia greater than 20% on two sequential determinations at least one month apart.

Measurement:

- Complete History and Physical Examination by a consulting neurologist prior to study entry.
- Screening ANA, Rheumatoid factor, thyroid function and HTLV-1 studies performed at study entry to rule out known competing causes of rheumatologic, endocrine, or viral myopathies.
- Laboratory studies: performed at baseline and monthly, consist of CBC; differential; Acute Care, Hepatic, and Mineral Panels; CK; LDH; Aldolase; Lactate; and Urinalysis.
- Clinical performance (manual muscle strength testing) and functional status assessment (timed muscle activities, functional grade) and health status assessment questionnaire performed at baseline and monthly intervals.

ADDENDA OR METHODOLOGIC CHANGES:

- Addendum # 1 (1/92): ICRS approved study size increase to 25 and addition of immune profiles obtained when the 2 muscle biopsies are obtained. A modification of the questionnaire items was made in order to distinguish health perceptions/health status in general from those that are condition-specific or related to myopathy.
- Three activities were added to further define upper and lower extremity strength and endurance: (1) maximum repetitions from a sitting to standing position; (2) upper extremity weight lifts using 1 - 35 pounds; and (3) maximum upper extremity lifts using maximum weight.
- The majority of the myopathy study patients have volunteered for NINDS protocol "Metabolic Studies of Muscle Weakness and Fatigue Using Exercise 31P Phosphorus Magnetic Resonance Spectroscopy" (#91-N-145). This study was closed June, 1992.
- As an addendum to "A Phase III Study of Zidovudine versus Zidovudine plus alpha-interferon in Patients with early HIV Infection" (#88-I-172), we collected one-time serum lactates on 10 patients in each of the three study groups (AZT alone, AZT + IFN, and IFN alone) to explore the relationship of lactate levels to myopathy.

- Results of the lactate collection mentioned above showed 17% of patients in each treatment arm had an asymptomatic elevated single lactate. Therefore, Protocol 88-I-172 was amended to obtain serum lactates every other month in all patients.
- Clinically indicated EMGs are obtained as of 7/92 one time on all new and existing patients on myopathy study. Correlation to biopsy results and manual muscle testing will be done.
- An NINDS intervention study is planned with NCNR collaboration, testing Carnitine (P.O.) for patients with biopsy-proven AZT-myopathy. Subjects will be recruited from NIAID and NINDS patients.
- NINDS protocol using IVIG for polymyositis is being offered to NCNR myopathy patients at the completion of protocol 91-I-142.

PROGRESS TO DATE:

Accrual:

- Initiated in May 1991.
- 70 patients screened to date (2 rescreened)
- 23 subjects out of the goal of 25 have been recruited, 16 of whom have completed the six month study. Two subjects are slated to begin in October 1992.
- As of September 1992, 7 people remain on-study. Plan to recruit 4 more subjects to replace the 4 subjects who refused second biopsy (amendment in progress).

Early Findings or Observations:

- Prolonged low dose, as well as high dose, AZT therapy may precede AZT mitochondrial myopathy.
- Discontinuation of AZT may improve mitochondrial myopathy, although in some instances myopathy remains stable or improves while continuing AZT.
- Increased lipid droplets and carnitive deficiency are observed on biopsy with AZT-myopathy.
- Clinical characteristics and muscle histology do not always correlate. For example, some patients who perform well clinically have severe mitochondrial myopathy on biopsy.

SIGNIFICANCE TO BIOMEDICAL RESEARCH AND THE NCNR:

Greater awareness of the natural history or response to clinically determined interventions for antiretroviral-associated myopathy will contribute to improved clinical management of this condition that is occurring more commonly as HIV infected individuals survive longer. This study will also provide information regarding how closely the clinical picture of this condition correlates with the anatomic and physiologic changes.

PROPOSED COURSE:

Data collection will proceed until all 25 subjects have been evaluated for the initially proposed 6-month duration of the study, at which time analysis will be carried out. Each subject who does not receive an investigational intervention for myopathy will be evaluated again at 12 months on all study parameters except muscle biopsy.

PUBLICATIONS:
None.

COLLABORATION:
Carried out in 11th floor NCNR exam room through Clinical Center 8th floor HIV Clinic involving collaboration with NIAID scientists and Study Coordinators, NINDS scientists and Fellows, and Clinical Center Nursing 8th floor AIDS Clinic Case Managers.

COMMENTS:
Study that NCNR developed based on identification of clinically relevant scientific opportunities followed by systematic review of the literature.

In order to answer new NCNR questions, NCNR primary data collection is augmented by NIAID study data.

November 5, 1992 rs
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